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Microsporidia and other opportunistic protozoa in patients with acquired immunodeficiency syndrome (AIDS)

Opportunistic infections are the consequence of the profound impairment of the host immune system induced by human immunodeficiency virus (HIV) and other immunosuppressive factors, and are caused by viruses, bacteria, fungi and protozoa. In HIV-infected patients, the protozoa causing severe illness belong to three phyla: Apicomplexa; Englenozoa; and Microspora. The classification of *Pneumocystis carinii,* a cause of pneumonia especially in children with AIDS, remains uncertain as this unicellular parasite, although referred to as a protozoan, also has the features of a fungus, as confirmed by molecular studies [1].

Within Apicomplexa, three species of coccidia – *Toxoplasma gondii, Cryptosporidium parvum* and *Isospora belli*, all known to produce infections in non-HIV-infected subjects – are particularly pathogenic in patients infected with HIV; the first microorganism causes severe necrotizing encephalitis, and the other two are generally involved in diarrhea and other gastrointestinal manifestations [2]. Diarrhea may also be due to cyanobacteria-like bodies, first described in 1986 in the stools of immunocompetent travellers returning from Morocco, India and Pakistan. Further studies have shown that these bodies correspond to the oocysts of a new coccidial parasite, *Cyclospora catenayensis,* and are found in Peruvian children as well as in AIDS patients [3]. Among Englenozoa (unicellular flagellates), the kinetoplastid *Leishmania infantum* appears to cause invasive infection in HIV-infected patients in endemic areas such as the Mediterranean basin [4]. This opportunistic infection shows the features of visceral leishmaniasis. Microspora were rarely reported in humans before the advent of AIDS, but with improvement and standardization of diagnostic methods, these microorganisms are becoming increasingly recognized to be an important cause of infection in HIV-infected patients. All incriminated species belong to the same order, Microsporidia, and five such species have been reported in AIDS patients. Some cases of keratoconjunctivitis caused by *Encephalitozoon hellem* were described in 1991 [5]. *Encephalitozoon cuniculi,* a species already known to cause encephalitis in mammals, and *Enceph. hellem* are also responsible for disseminated infection owing to their localization within macrophages. Three cases of myositis are known to have been caused by *Trachipleistophora hominis* [6]. Of all microsporidial infections, those affecting the intestines are the most frequently seen in HIV-infected patients. Two species, *Enterocytozoon bieneusi* [7] and *Encephalitozoon intestinalis* [8], are involved in gastrointestinal diseases; however, *Entero. bieneusi* is restricted to epithelial cells whereas *Enceph. intestinalis* infects macrophages in the lamina propria and is thereby disseminated to the urinary, hepatobiliary and respiratory tracts [9]. Both species are responsible for diarrhea, malabsorption, weight loss, nausea and abdominal cramping in up to 40% of AIDS patients presenting with these features in the absence of other enteric pathogens, and approximately 80% of cases of microsporidiosis are caused by *Entero. bieneusi* [10].

A recent evaluation of the prevalence of enteric pathogens in an HIV-infected population with gastrointestinal symptoms indicated that intestinal microsporidia are the major cause of infection [11], and were found in 39% of 141 AIDS patients with diarrhea. An identical proportion of patients were infected by *Cryptosporidium* as by cytomegalovirus (both 23.4%). *Mycobacterium avium* complex and adherent bacteria causing damage to the subjacent epithelium were reported in 13.5% and 12.8% of patients, respectively. *Isospora, Giardia, Histoplasma, Shigella* and adenovirus were less frequently observed, affecting only 0 to 2.1% of patients. Some patients in this series were concomitantly infected by more than one relevant infecting agent.

Unfortunately, there is as yet no known therapy

effective against *Entero. bieneusi* and *Cryptosporidium,* although some patients with cryptosporidiosis have shown improvement with paromomycin. Such a lack of treatment probably contributes to the increasing prevalence of these infections.

Opportunistic pathogens tend to spread from their primary site in advanced stages of immunodeficiency and, for some, this dissemination results in generalized disease. The pathogenicity correlates with depletion of CD4 plus T-lymphocyte counts (< 50 cells/mm^3). Recent data indicate that the consequent decrease in the production of activating factors such as interferon (IFN) γ contributes to the proliferation and dissemination of pathogens by macrophages. Didier [12] has recently shown that IFN-γ in combination with lipopolysaccharide induces murine macrophages to kill *Enceph. cuniculi* through the nitric oxide-dependent mechanism that is also involved in the destruction of viruses, bacteria and fungi as well as *Toxoplasma* and *Leishmania* [13]. It is noteworthy that the rare cases of focal microsporidiosis observed in immunocompetent patients are limited to immunoprivileged sites, exemplified by ocular infections caused by *Nosema corneum* and *Nosema ocularum* [14,15].

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